Cancer as an evolutionary process

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Main points

1. Cancer is an evolutionary process

2. Cancer genomics allows to look under the hood of this process

3. Treating cancer using its own evolutionary mechanisms
Evolution

mutations

diversity

selection
Evolution

mutations

diversity

selection

environment
Evolution

mutations

diversity

selection

environment

gradual change

accumulation of mutations
Mutant is new normal

- mutations
- diversity
- selection

- gradual change
- accumulation of mutations

new phenotype is acquired
Cancer = evolution

Recall, for example, the disease of familial adenomatous polyposis (FAP; see Section 7.11), in which an individual inheriting a mutant form of the APC tumor suppressor gene is prone to develop anywhere from dozens to more than a thousand polyps in the intestine (see Figure 7.22). With a certain low but measurable frequency, one or another of these polyps will progress spontaneously into a carcinoma. (The multiplicity of polyps in these patients and the low conversion rate of polyps to carcinomas—estimated to be ~2.5 events per 1000 polyps per year—effectively preclude association of a carcinoma with a particular precursor polyp.)

The development of carcinomas in other organ sites throughout the body is thought to resemble, at least in outline, the multi-step progression observed in the colon (see, for example, Figure 11.8A). Many of these other tissues, such as the breast, stomach, lungs, prostate, and pancreas, also exhibit growths that can be called hyperplastic, dysplastic, and adenomatous, and these growths would seem to be the benign precursors of the carcinomas that arise in these organs. However, the histopathological

**Figure 11.8** Multi-step tumorigenesis in a variety of organ sites

(A) The pathogenesis of carcinomas is thought to be governed by very similar biological mechanisms operating in a variety of epithelial tissues. Accordingly, multi-step tumorigenesis involving similar histological entities has been proposed to progress along parallel paths in these various organ sites. These similarities are obscured by the fact that the nomenclature is quite variable from one tissue to another. CIS, carcinoma in situ; CIN, cervical intraepithelial neoplasia; DCIS, ductal carcinoma in situ; PIN, prostatic intraepithelial neoplasia.

(B) Because more aggressive growths often overgrow their more benign precursors, it is rare to see the multiple states of tumor progression coexisting in close proximity, as is the case in this lung carcinoma. Importantly, while the close juxtaposition of the aberrant growths suggests some relationship among them, an image like this provides no definitive evidence of precursor–product relationships between these various abnormal tissues. (A, courtesy of W.K. Hong. B, courtesy of A. Gonzalez and P.P. Massion.)
Cancer = evolution

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Acquired phenotypes of cancer

The Hallmarks of Cancer

Douglas Hanahan∗ and Robert A. Weinberg†
Acquired phenotypes of cancer acquired *mutations*

Mutation targets

*tumor suppressors* and *oncogenes*
Acquired phenotypes of cancer acquired *mutations*

Mutation targets *tumor suppressors* and *oncogenes*
Acquired phenotypes of cancer acquired *mutations*

Mutation targets *tumor suppressors* and *oncogenes*
Mutation targets tumor suppressors and oncogenes [drivers]
Oncogenes and tumor suppressors
[drivers]

• Oncogenes -- need to be activated
  – by mutations (within a gene or regulatory regions)
  – by chromosomal alterations
  – overexpression/modifications

• Tumor suppressors -- need to be inactivated
  - mutations, chromosomal loss, modifications
Cancer: series of driver mutations

- **Initiating mutation**
  - This is the first mutation that gives a cell a proliferative or survival advantage, allowing it to outcompete its neighbors. It can occur as a result of DNA replication errors, environmental factors, or inherited mutations.

- **Second mutation**
  - The second mutation occurs in the population of cells that have already accumulated the first mutation. It confers additional traits that further enhance the cell's ability to proliferate and survive.

- **Third mutation**
  - Following the second mutation, a third mutation may occur, leading to even greater proliferation and survival advantages. This results in a larger and more diverse clone.

- **Fourth mutation**
  - This mutation, much like the previous ones, enhances the proliferative and survival capabilities of the cell. The resulting clone eventually dominates the tissue environment, overshadowing genetically less favored neighbors.

- **Clonal expansions**
  - Each new mutation results in a larger clone of cells with the same mutation(s). This process repeats over time, with each expansion occurring at roughly the same rate, leading to a series of clonal successions.

- **Simplified model**
  - The Darwinian model of cancer progression simplifies the process by focusing on the role of driver mutations. However, it is important to note that the process is more complex, involving the accumulation of various mutations and their interactions over time.

- **Multi-step tumor progression**
  - The model takes into account multi-step tumor progression, where each step involves the accumulation of mutations that contribute to cancer development. This is a critical aspect of understanding the evolution of cancer.

- **Darwinian evolution**
  - Darwinian evolution helps explain the sequence of events leading to cancer development. It underscores the idea that cancer is an evolutionary process, driven by the accumulation of mutations and the subsequent selection of cells with advantageous traits.

- **Promoter methylation**
  - As discussed in Chapter 7, promoter methylation, a type of epigenetic alteration, can play an important role in cancer progression. These changes can drive the inactivation of tumor suppressor genes, contributing to the development of cancer.

- **Importantly**
  - The model is simplified for clarity, but in reality, the process is complex and involves the interplay of various genetic and epigenetic factors.

- **Figure 11.15**
  - The figure illustrates the clonal expansion model over time, showing the accumulation of mutations and the proliferation of clones. It visually represents the series of driver mutations and the resulting clonal expansions.
Cancer: is hard to stop because it’s an evolutionary process
Main points

1. Cancer is an evolutionary process

2. Cancer genomics allows to look under the hood of this process

3. Treating cancer using its own evolutionary mechanisms
Mutations: germline and somatic

Large-scale alterations of the cell genome. Indeed, such alterations were noted as early as 1892, specifically in cancer cells. Today, we know that cancer cells often exhibit aberrantly structured chromosomes of various sorts, the loss of entire chromosomes, the presence of extra copies of others, and the fusion of the arm of one chromosome with part of another. These changes in overall chromosomal configuration expand our conception of how mutations can affect the genome: since alterations of overall chromosomal structure and number also constitute types of genetic change, these changes must be considered to be the consequences of mutations (Sidebar 1.2). And importantly, the abnormal chromosomes seen initially in cancer cells provided the first clue that these cells might be genetically aberrant, that is, that they were mutants (see Figure 1.11).

The normal configuration of chromosomes is often termed the euploid karyotypic state. Euploidy implies that each of the autosomes is present in normally structured pairs and that the X and Y chromosomes are present in the numbers appropriate for the sex of the individual carrying them. Deviation from the euploid karyotype—the state termed aneuploidy—is seen, as mentioned above, in many cancer cells. Often this aneuploidy is merely a consequence of the general chaos that reigns within a cancer cell. However, this connection between aneuploidy and malignant cell proliferation also hints at a theme that we will return to repeatedly in this book: the acquisition of extra copies of one chromosome or the loss of another can create a genetic configuration that somehow benefits the cancer cell and its agenda of runaway proliferation.

Mutations causing cancer occur in both the germline and the soma.
Cancer genomics

• Get a sample of cancer => sequence
• Get a sample of normal tissue (from the same patient) => sequence
Cancer
Finding driver events
Rates of somatic mutation vary across cancers: [G.Getz]

Estimated number of changes in proteins

Hematologic Childhood

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<th>MM</th>
<th>OV</th>
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Estimated number of changes in proteins

C->T
C->A
C->G
T->C
T->A
T->G
Figure 1 | Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs. Each dot corresponds to a tumour–normal pair, with vertical position indicating the total frequency of somatic mutations in the exome. Tumour types are ordered by their median somatic mutation frequency, with the lowest frequencies (left) found in haematological and paediatric tumours, and the highest (right) in tumours induced by carcinogens such as tobacco smoke and ultraviolet light. Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions, as indicated in the legend on the left. See also Supplementary Table 2.
Cancer genomics

- Whole-genome sequences (cancer vs normal)
- Whole-exome sequences (cancer vs normal)
- Copy-number alterations

Chromosomal alterations
Cancer deletion
Somatic Copy Number Alterations (SCNAs)
Finding oncogenes and tumor suppressors
Deletions  Amplifications

tumor suppressors and oncogenes
Cancer genomics

Finding new oncogene and tumor suppressors
Whole mutational landscape of cancer
Precision medicine:
mutations in each patient
Main points

1. Cancer is an evolutionary process

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3. Treating cancer using its own evolutionary mechanisms
Cancer genomics

100-400 amino acid substitutions
10-40 chromosomal alterations

2-5 drivers

the rest are passengers

Can some passengers

... be deleterious to cancer cells?
... affect progression?
Are cancers weighted down by passengers?

Studies of cancer biology and genomics have mainly focused on recurrent driver mutations in key oncogenes and tumour suppressor genes, as these are known to have major roles in tumorigenesis and cancer progression. However, these driver mutations are vastly outnumbered by passenger mutations, which are often assumed to be biologically neutral.

A new computational study suggests that passenger mutations may have detrimental effects on tumour fitness, with therapeutic implications. Random unselected mutations are expected to be, on average, mildly deleterious (that is, they confer a small selective disadvantage). So, Leonid Mirny and colleagues incorporated deleterious passenger mutations into their computer simulations of tumour evolution. In their model, each cancer cell can stochastically die or divide, and the cell divisions can be accompanied by the frequent acquisition of a deleterious passenger mutation or the rare acquisition of a growth-promoting driver mutation. The simulations resulted in population dynamics in which tumours grew in a sawtooth manner: each acquisition of a driver event resulted in the rapid expansion of the tumour cell population, which was followed by a gradual decline in cell number owing to passenger mutation accumulation until the next driver mutation occurred. Importantly, accounting for deleterious passenger mutations recapitulated some known features of tumour biology, such as dormancy and regression, that are not seen in simpler simulations.

Interestingly, despite the deleterious nature of the simulated passenger mutations, large numbers of passenger mutations accumulated and spread throughout the tumour cell population. This partly occurred by mechanisms that are known from population genetics studies. For example, the positive selection of cells containing driver mutations can increase the frequency of passenger mutations co-occurring in these cells (an effect that is known as genetic hitch-hiking). Overall, this indicates that even mutations that are found throughout a large proportion of cells in a particular tumour might actually exert a negative fitness effect.

So, is there evidence that passenger mutations found in clinical tumours can be genuinely deleterious or might real tumours retain only selectively neutral passenger mutations? The authors assessed the deleteriousness of passenger mutations in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. They used the PolyPhen program, which scores deleteriousness according to the extent to which the mutation has been avoided (selected against) during organismal evolutionary history. On average, these passenger mutations were indeed moderately deleterious, and substantially more so than single-nucleotide polymorphisms underlying normal human population variation. However, it is worth noting that deleteriousness of a mutation during normal organismal evolution might not fully reflect the fitness effects on cancer cells, which typically have altered cell death and checkpoint mechanisms.

Finally, the authors ran simulations and found that enhancing the detrimental effects of passenger mutations — such as by reducing the ability of cancer cells to buffer deleterious mutations — resulted in sustained tumour regression. In practice, such buffering mechanisms include the proteasome and chaperone systems. As pharmacological inhibitors of these systems have been developed that show antitumour activity in some settings, it will be interesting to determine the extent to which sensitivity to these agents is conferred by many accumulated passenger events versus a few key oncogenic mutations.
Passengers hitchhike to fixation
Hitchhiking passengers

Neutral or deleterious
Passenger load negatively correlates with metastasis
New Experiment: Her2+ breast cancer mouse model:
- mildly elevated mutation rate (H2AX+/-)
- normal mutation rate (control)

Passengers slowdown cancer
Passenger-based treatment

- Mutagenic chemo
  - requires very high mutation rate
  - likely relapse

Increase mutation rate
Passenger-based treatment

Make passengers more damaging

Going with evolution, not against it

[hackers lingo: passenger load is an exploit]
Response to immunotherapy is associated with mutational load

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

Figure 2. Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.
Work in progress…

1. Passenger mutations can be damaging!
2. Passenger load is a potential biomarker of response to chemo- and immuno-therapy
3. Passengers may be responsible for other cancer phenotypes

NEED :: More patient info + genotypes (PLM?)
Main points

1. Cancer is an evolutionary process

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3. Treating cancer using its own evolutionary mechanisms
Tug-of-war between driver and passenger mutations in cancer and other adaptive processes

Christopher D. McFarland*, Leonid A. Mirny*, Kirill S. Korolev, Gregory Kryukov, Michael Sherman, Julia Yaglom, Jonathan Wojtkowiak, David Basanta, Michael Sherman, Leonid Mirny and Jacob Scott

Experiments

Metastatic potential

Genomics

Nature Reviews Cancer | AOP, published online 7 March 2013; doi:10.1038/nrc3488

Weighed down by passengers?